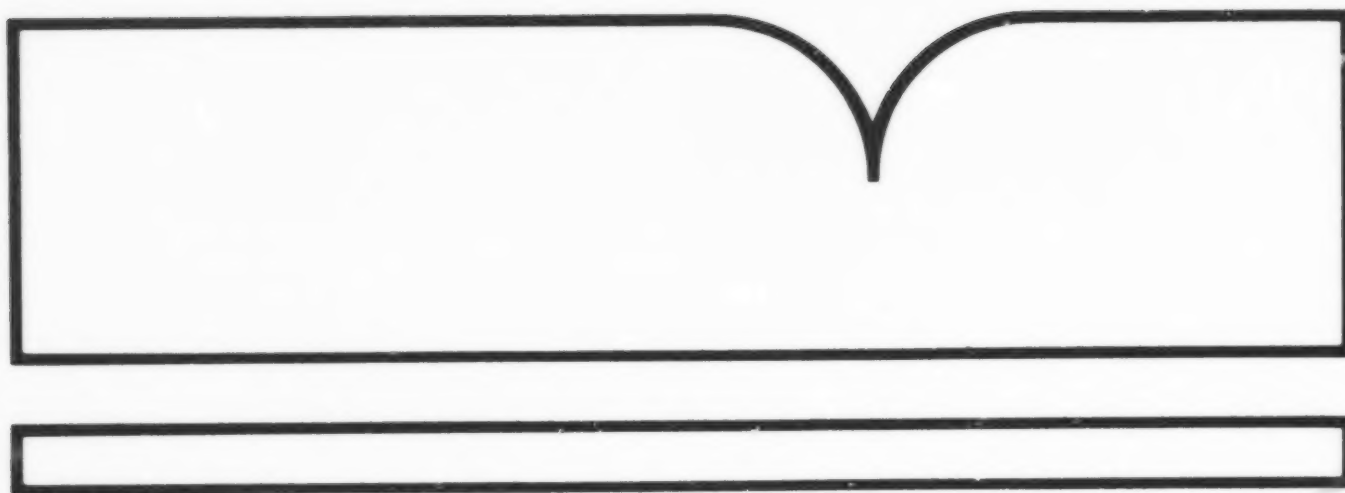


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Health and Environmental
Effects Profile for Methylcyclohexane

(U.S.) Environmental Protection Agency
Cincinnati, OH

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR METHYLCYCLOHEXANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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SPRINGFIELD, VA 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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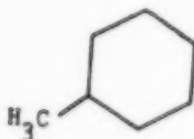
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CNS	Central nervous system
LD _{Lo}	Lowest lethal dose
NOEL	No-observed-effect level
OSHA	Occupational Safety and Health Administration
ppb	Parts per billion
ppbC	Parts per billion carbon
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Methylcyclohexane is also known as hexahydrotoluene and cyclohexyl methane (NIOSH, 1983). The structure of the compound is depicted below:



Molecular formula: C_7H_{14}

Molecular weight: 98.21

The Chemical Abstracts Service (CAS) Registry number for this compound is 108-87-2.

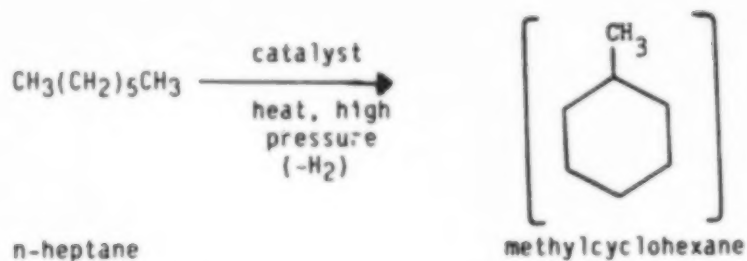
1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methylcyclohexane is a colorless liquid with a pungent odor at room temperature. Some of the physical properties are listed below:

Specific gravity:	0.769 (Hawley, 1977)
Boiling point:	100.8°C (Hawley, 1977)
Melting point:	-126.9°C (Hawley, 1977)
Solubility at 25°C:	14 mg/kg in water; soluble in acetone, benzene, ether and carbon tetrachloride (McAuliffe, 1966)
Log octanol/water partition coefficient:	2.76 (Hansch et al., 1968)
Vapor pressure:	40 mm Hg at 22°C (ACGIH, 1980)
Evaporation rate:	6.7 mg/min/cm ² at 45°C (Treon et al., 1943b)
Flash point:	-18°C (Hawley, 1977)
Autoignites at:	270.8°C (Hawley, 1977)

1.3. PRODUCTION DATA

Methylcyclohexane is obtained from petroleum. It can also be prepared by the following reaction (Allinger et al., 1971):



Methylcyclohexane is produced by the Phillips Chemical Company in Hutchinson, Texas (SRI, 1983; U.S. EPA, 1983). Production data for the United States were unavailable.

1.4. USE DATA

Methylcyclohexane is used as a solvent for cellulose ethers and in organic synthesis (Hawley, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Methylcyclohexane may be released into the environment from vehicular emissions, organic solvents, oil spills or manufacturing processes.

The primary fate of methylcyclohexane should be transport into the atmosphere where photolysis should be rapid (Smith and Harper, 1982). This compound has been shown to react with O_3 and NO under simulated environmental conditions. The NO photooxidation rate of pure methylcyclohexane (2 ppm/1 ppm NO_x), tested in an irradiation chamber with UV light, was reported as ~7 ppm/minute (Yanagihara et al., 1977). A mean photooxidation rate for pure hydrocarbons with O_3 was 1.77 ppb/minute. During irradiation in plastic Tedlar bags with natural sunlight, 45% of methylcyclohexane was lost within 6 hours, indicating that the compound exhibited relatively high reactivity (Kopczynski et al., 1972). The dynamic nature of the open atmosphere may alter the reactivity of this compound in the environment compared to its reactivity under laboratory experimental conditions (Kopczynski et al., 1972; Yanagihara et al., 1977).

The fate of methylcyclohexane in soil or water may be influenced, in part, by microbial degradation. Buswell and Turtshuk (1968) demonstrated that methylcyclohexane was fairly resistant to oxidative attack by Corynebacterium sp. Tonge and Higgins (1974) proposed that methylcyclohexane could be oxygenated by Nocardia petroleophila to form methylcyclohexanol with subsequent dihydrogenation to yield the ketone, 3-methylcyclohexanone. Pure cultures of Nocardia sp. and Pseudomonas sp., isolated from estuarine mud flats, littoral sediments and soil, were able to use methylcyclohexane as a sole carbon and energy source (Tonge and Higgins, 1974; Anderson et al., 1980; Stirling and Watkinson, 1976; Cundell and Traxler, 1973); however, these data do not imply that similar degradation will occur in the natural environment.

Volatilization may influence the transport of methylcyclohexane from the aqueous media. Smith and Harper (1982) measured the relative volatilization rate of methylcyclohexane from water compared to oxygen as 0.48 ± 0.15 . The estimated volatilization half-lives in the environment were 7 days in ponds, 1.5 days in rivers and 6 days in lakes.

3. EXPOSURE

STORET contained 17 observations for methylcyclohexane in aqueous and sediment samples collected in 1979. The concentrations for nine samples from ambient water ranged from 5.0-100.0 $\mu\text{g}/\text{L}$, with a mean of 15.56 $\mu\text{g}/\text{L}$. Concentrations reported for eight samples from the sediment ranged from 5.0-1580.0 $\mu\text{g}/\text{kg}$, with a mean of 256.875 $\mu\text{g}/\text{kg}$.

A plethora of monitoring data for methylcyclohexane in the atmosphere was available. A review of many of the studies suggests that ambient levels of methylcyclohexane are generally greater in urban areas and in the immediate vicinity of manufacturing facilities than in rural areas. For example, Lonneman et al. (1979) reported concentrations of 4.5-196.8 ppm for urban air in Houston, Texas, and Seila (1979) reported 1.3-9.3 ppbC for non-urban ambient Houston air. Concentrations of 5.5 $\mu\text{g}/\text{m}^3$ were reported for air surrounding a large automotive plant, and 1.0-1.5 $\mu\text{g}/\text{m}^3$ were measured 150 km downwind from the site (Sexton and Westberg, 1980). Arnts and Meeks (1981) measured higher levels of methylcyclohexane downwind from a Texaco refinery (36.5 ppbC), and in downtown Tulsa, Oklahoma (8.2 ppbC) than in air sampled from suburban (6.6 ppbC) and rural (4.2 ppbC) areas in the same vicinity. It appears that methylcyclohexane is ubiquitous due to automotive emissions (Hampton et al., 1982), but occurs at greater concentrations in and around urban or industrial areas.

4. PHARMACOKINETICS

4.1. ABSORPTION

Studies examining the absorption of methylcyclohexane were not located in the available literature (see Appendix); however, it can be inferred from the metabolism study of Elliott et al. (1965) that methylcyclohexane is absorbed from the gastrointestinal tract of rabbits following oral administration.

4.2. DISTRIBUTION

Following administration by gavage of 2.10, 2.26 or 2.41 μ moles ^{14}C -methylcyclohexane/kg bw to rabbits, 3.8, 5.9 and 2.8%, respectively, of the radioactivity was recovered in the tissues ~60 hours after dosing (Elliott et al., 1965).

4.3. METABOLISM

Elliott et al. (1965) reported that ring fission is a minor metabolic route (~5%). In rabbits receiving doses of 2.1, 2.26 or 2.41 μ moles of uniformly labeled ^{14}C -methylcyclohexane/kg bw, 64.5, 54.2 and 77.4%, respectively, of the administered radioactivity was excreted in the urine conjugated with glucuronic acid, and 0.4, 0.5 and 0.7%, respectively, appeared in the feces by ~60 hours after dosing. About 10% of the unchanged compound was expired in the air and ~5% was expired as $^{14}\text{CO}_2$. The $^{14}\text{CO}_2$ was thought to result from oxidative cleavage of the ring. The approximate percentages of the urinary metabolites were: trans-4-methylcyclohexanol, 14.7; cis-4-methylcyclohexanol, 2.4; trans-3-methylcyclohexanol, 10.5; cis-3-methylcyclohexanol, 11.5; trans-2-methylcyclohexanol, 1.2; and cis-2-methylcyclohexanol, 0.5, expressed as percent of dose.

Methylcyclohexane was hydroxylated in vitro to all its isomeric alcohols in the presence of NADPH, oxygen and hepatic microsomes of rats, mice,

rabbits or guinea pigs. No significant change in the hydroxylation pattern was observed in animals pretreated with phenobarbital when compared with untreated controls. All incubations with the hepatic microsomes of different species yielded 3-methylcyclohexanol as the major hydroxylation product. Although there was a high ratio of hydroxylation at the secondary CH bonds, the preferred site of attack was the tertiary CH bond (Frommer et al., 1970).

4.4. EXCRETION

Elliott et al. (1965) administered single doses of 2.1, 2.26 or 2.41 μ moles of uniformly labeled ^{14}C -methylcyclohexane/kg bw to rabbits by gavage. Within 58-68 hours, 64.5, 54.2 and 77.4%, respectively, of the administered dose was excreted in the urine; 0.4, 0.5 and 0.7% was excreted in the feces; 15.9, 1.3 and 4.4% was expired as methylcyclohexane; and 5.0, 3.3 and 8.6% was expired as $^{14}\text{CO}_2$.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of methylcyclohexane were not located in the available literature. This compound is not scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Pertinent data regarding the mutagenic potential of methylcyclohexane were not located in the available literature.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic potential of methylcyclohexane were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects associated with exposure to methylcyclohexane were not located in the available literature.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Treon et al. (1943a) exposed a rhesus monkey to 372 ppm methylcyclohexane by inhalation for 6 hours/day, 5 days/week over a period of 70 days. The monkey was killed 2 months after cessation of exposure for gross and histopathologic examination. Exposure to methylcyclohexane produced no overt signs of toxicity, changes in hematologic values (measured weekly), or histopathologic effects.

In similar experiments with rabbits, Treon et al. (1943a) exposed groups of four rabbits to methylcyclohexane by inhalation for 6 hours/day, 5 days/week at the following concentrations and durations: 241, 372 or 1162 ppm for 10 weeks; 2886 ppm for 3 weeks; 5567 ppm for 4 weeks; 7308 or 10,054 ppm for 2 weeks. Several groups of control animals were sham-exposed in a similar manner. Body weights and hematologic values were checked weekly;

surviving animals were killed for histopathologic examination 2 months after cessation of exposure. No hematologic changes were seen in any of the exposed groups. No signs of toxicity or histopathologic effects were observed in rabbits exposed to ≤ 1162 ppm. Slight, unspecified histopathologic changes were observed in the livers and kidneys of rabbits exposed to 2886 ppm, but no overt signs of toxicity were apparent. Higher concentrations of methylcyclohexane produced signs of CNS toxicity ranging from slight lethargy at 5567 ppm to convulsions and light narcosis at 10,054 ppm. No deaths occurred at concentrations ≤ 5567 ppm, 1 of 4 rabbits died at 7308 ppm, and all 4 rabbits died at 10,054 ppm.

5.6. OTHER RELEVANT INFORMATION

The inhalation experiments conducted by Treon et al. (1943a), discussed in Section 5.4., give some information on the acute toxicity of methylcyclohexane. Death occurred among three groups of four rabbits exposed repeatedly to concentrations of 7308 or 10,054 ppm, 6 hours/day, 5 days/week for 2 weeks or once to 15,227 ppm methylcyclohexane for 70 minutes. All rabbits exposed to the two higher concentrations died, and 1 of 4 exposed to 7308 ppm died. Severe convulsions, rapid narcosis, labored breathing, salivation, conjunctival congestion, coughing, sneezing and diarrhea were observed in rabbits exposed to 15,227 ppm methylcyclohexane by inhalation for 70 minutes. Convulsions, light narcosis, labored breathing, salivation and conjunctival congestion were observed in rabbits exposed to 10,054 ppm and lethargy and impaired coordination was observed at 7308 ppm.

Lazarew (1929) observed that inhalation of 7500-10,000 ppm methylcyclohexane for 2 hours caused prostration in mice, and inhalation of 10,000-12,500 ppm for 2 hours was fatal.

Kinthead et al. (1979) reported that exposure of rats and mice by inhalation to 6564 ppm methylcyclohexane resulted in immediate hyperactivity, "whereas 4200 ppm appeared to be a safe 1-hour exposure limit". Dogs exposed to 4071 ppm for one hour had no behavioral or histopathological effects. Based on these and other data, Kinthead et al. (1979) recommended 4000 ppm atmospheric methylcyclohexane as the 1-hour emergency exposure limit for humans.

In acute oral experiments, Treon et al. (1943b) administered single doses of methylcyclohexane to rabbits by gavage and observed the animals for at least 14 days. Four rabbits given doses of 1.0-4.0 g/kg survived, whereas four rabbits given doses of 4.5-10 g/kg died. Hence, the minimum lethal dose for rabbits appeared to be between 4.0 and 4.5 g/kg. The animals given ≥ 4.5 g/kg had severe diarrhea. No evidence of acute CNS toxicity (convulsions or narcosis) was observed at any dose, although the rabbits were lethargic. No hematologic changes were observed.

Methylcyclohexane was found to increase the permeability of the membranes of human lung fibroblasts in vitro (Thelestam et al., 1980).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The concentration of methylcyclohexane which caused no mortality in rainbow trout, Salmo gairdneri, was <0.8 mg/l (Klein et al., 1975). In flagfish, Jordanelia floridae, methylcyclohexane caused mortality at levels of 0.83-1.85 mg/l (Klein et al., 1975).

In a study of the aquatic toxicity of components of JP-9 jet fuel, Jenkins et al. (1977) exposed golden shiners, Notemigonus chryssoleucas, to emulsified methylcyclohexane for 96 hours. The static LC_{50} values determined for 48, 72 and 96 hours of exposure in hard water (100 mg $CaCO_3$ /l) were 126, 90 and 72 μ l/l (97, 69 and 55 mg/l), respectively. In these assays the methylcyclohexane solution was removed every 24 hours. The LC_{50} s following exposure in soft water (25 mg $CaCO_3$ /l) when the test solutions were not renewed were 81 μ l/l (62 mg/l) for all intervals up to 96 hours. These data suggest that methylcyclohexane evaporates from the aqueous environment quite rapidly. The LC_{50} value of unemulsified methylcyclohexane (standing pool bioassay) was 240 μ l/l (185 mg/l) for exposures up to 96 hours when the solution was not renewed.

6.2. CHRONIC EFFECTS

Based on studies exposing rainbow trout, S. gairdneri, to methylcyclohexane at 0.01 (control), 0.31, 0.80, 0.84 and 1.19 mg/l for 23 days, Jenkins et al. (1977) reported mortality to be 3, 3, 3, 23 and 40%, respectively. Methylcyclohexane at 0.8 mg/l was regarded as the critical level for chronic lethal effects, but a level of 0.84 mg/l caused substantial mortality. Based on the limited mortality data (mortality was only 40% in the highest dose groups) the LC_{50} for this 23-day study was estimated to be near 1.3 mg/l for rainbow trout.

Methylcyclohexane at levels up to 0.83 mg/l had no effect on the hatchability of eggs of J. floridae (Klein et al., 1975; Jenkins et al., 1977). Mortality among flagfish fry (n=5) was 100% after 7 days of exposure to 1.85 mg methylcyclohexane/l in a static bioassay. However, no toxic effects (fish lengths and weights) or mortality were reported among fry exposed to concentrations of methylcyclohexane up to 0.83 mg/l for 87 days (Jenkins et al., 1977).

6.3. PLANT EFFECTS

Pertinent data regarding the toxic effects of methylcyclohexane on aquatic plants were not located in the available literature.

6.4. RESIDUES

Jenkins et al. (1977) reported a level of ~1.19 mg methylcyclohexane/g wet fish tissue in flagfish, J. floridae, dying as a result of exposure to 1.85 mg/l for 7 days. Based on tissue levels in fish surviving exposure at 0.83, 0.67 and 0.34 mg/l for 87 days, a linear relationship between exposure level and body burden was demonstrated. Tissue levels of ~0.5 mg methylcyclohexane/g wet tissue were tolerated by flagfish. The lethal body burden of methylcyclohexane is, therefore, between 0.5 and 1.19 mg/g wet tissue in the flagfish.

In rainbow trout (S. gairdneri) exposed to methylcyclohexane at ~0.30 mg/l for 42 days, the concentration of the compound in wet tissue was ~0.05 mg/g (Jenkins et al., 1977). A bioconcentration factor of ~150 was suggested. The level of methylcyclohexane in the trout dropped rapidly during a 12-hour post-exposure period in clean water, indicating rapid clearance.

Methylcyclohexane residues, estimated to be 2 µg/kg, were detected in rainbow trout, S. gairdneri, taken from the Colorado River below Hoover Dam

(Hiatt, 1983). Carp, Cyprinus carpio, taken in Las Vegas, Nevada, and large mouth bass, Micropterus salmoides, taken from the San Joaquin River in California also contained detectable levels of methylcyclohexane. Both rainbow trout and flagfish, J. floridae, were reported to concentrate methylcyclohexane 150-fold from the environment (Klein et al., 1975).

6.5. OTHER RELEVANT INFORMATION

Additional data pertinent to the toxicity of methylcyclohexane on aquatic organisms were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The TLV for substances in workroom air for methylcyclohexane was reported as 400 ppm, and the STEL as 500 ppm (ACGIH, 1980). According to the Code of Federal Regulations (1981), OSHA has set a TWA standard for air at 500 ppm methylcyclohexane.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of methylcyclohexane were not located in the available literature (see Appendix).

B. RISK ASSESSMENT

Pertinent data regarding the carcinogenic, mutagenic or teratogenic potential of methylcyclohexane were not located in the available literature.

There is no information regarding the effects of chronic exposure to methylcyclohexane. The subchronic inhalation study in one rhesus monkey by Treon et al. (1943a) appeared to identify a NOEL of 363 ppm (6 hours/day, 5 days/week for 10 weeks). In the same study, Treon et al. (1943a) exposed three groups of four rabbits to 241, 372 or 1162 ppm methylcyclohexane for 6 hours/day, 5 days/week for 10 weeks and found no effects attributable to treatment. Four rabbits exposed to 2886 ppm methylcyclohexane for 6 hours/day, 5 days/week for 3 weeks had slight histopathologic changes in the liver and kidneys, leading the authors to conclude that the safe concentration for prolonged exposure of rabbits to methylcyclohexane is between 4.57 and 11.35 mg/l (1162 and 2886 ppm, respectively). The adequacy of these inhalation studies to serve as the basis for an ADI for chronic oral exposure is questionable. These studies involved relatively short exposure periods (70 days or less); few animals were studied; and histopathologic examinations were not performed at the end of the exposure period, but instead only after a post-treatment observation period of 2 months. Furthermore, it is unclear whether the effects of oral exposure would be similar to those of inhalation exposure.

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
TSCAPP
AQUIRE
EPCASR
Chemical Industry Notes

These searches were conducted in May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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